LIMBAL TRANSPLANTATION AFTER CHEMICAL INJURIES OF THE EYE

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ABSTRACT

Purpose: To illustrate the benefit of limbal stem cell transplantation in three eyes with severe ocular surface failure due to chemical burns.

Methods: In two patients with monocular corneal scarring and vascularization after chronic chemical burns, a limbal tissue autograft was transferred from the unaffected fellow eye. A complete superficial keratectomy was performed on the host eye. One patient with bilateral ocular surface disorder received an eccentrically trephined corneolimbal allograft. To prevent immunologic rejection of the transplanted limbus, this patient was treated with systemic Ciclosporin A.

Results: Postoperatively the limbal autografts grew a normal epithelium on the recipient eye with less vascularization and scarring. Our two patients reported a significant reduction in symptoms (redness, pain, photophobia) and an improved visual acuity. The corneolimbal allograft has remained clear for five months postoperatively.

Conclusion: In strictly unilateral conditions of limbal deficiency, transplantation of healthy limbal tissue from the normal fellow eye may result in a stable ocular surface and a quiet and comfortable eye. Transplantation of an eccentrically trephined corneolimbal allograft under systemic Ciclosporin A cover may be an option in the rehabilitation of patients with severe bilateral stem cell deficiencies.

RESUME

But: Démontrer le bénéfice de la transplantation de cellules souches limbiques dans trois yeux avec sévères cicatrices de la surface oculaire dûes à un traumatisme chimique.

Méthodes: Une autogreffe tissulaire limbique a été prise de l'oeil sain dans deux patients avec cicatrice et vascularisation unilatérales après brûlure cornéenne. Une kératectomie superficielle complète a eté réalisée sur l'oeil receveur.

Un patient présentant une brûlure cornéenne bilatérale a reçu une allogreffe cornéolimbique. Pour réduire les risques de réaction immunitaire contre le tissu transplanté, ce patient a été traité par administration systémique de Ciclosporine A.

Résultats: En post-opératoire, les autogreffes limbiques ont généré un épithélium normal dans l'oeil receveur avec moins de vascularisation et de tissu cicatriciel. Nos deux patients présentaient une baisse significative des symptomes (rougeur, douleur, photophobie) et une amélioration de l'acuité visuelle. Le greffon cornéolimbique était toujours clair cinq mois après l'intervention.

Conclusion: Dans des cas unilatéraux de déficience limbique, l'utilisation de greffons limbiques sains de l' oeil adelphe peut donner une surface oculaire stable et un oeil calme et comfortable. La transplantation d'une allogreffe cornéolimbique sous couverture de Ciclosporine A par voie générale doît être envisagée dans la réhabilitation de patients avec une déficience sévère de cellules souches.

SAMENVATTING

Doel: Het voordeel van limbale stamceltransplantatie illustreren in drie ogen met ernstig cornea-oppervlakte falen door chemische verbranding.

Methode: Bij twee patiënten met unilaterale corneaverlittekening en bloedvatingroei na chemische verbranding werd limbaal weefsel getransplanteerd afkomstig van het onbeschadigde andere oog. Een volledige oppervlakkige keratectomie van het receptor oog werd uitgevoerd. Eén patiënt met bilaterale corneaverbranding kreeg een excentrisch getrepaneerde corneolimbale allogreffe. Om immunologische afstoting van de getransplanteerde limbus tegen te gaan werd bij deze patiënt langs algemene weg Ciclosporine A toegediend.

Resultaat: Postoperatief groeide vanuit de limbale autogreffen een normaal epitheel over de receptorcornea, met afname van de bloedvatingroei en lit-

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tekenvorming. Onze twee patienten genoten opmerkelijk minder subjectieve hinder en een betere visus. Bij de patient met de bilaterale corneaverbranding was de corneolimbale allogreffe vijf maanden na de ingreep nog steeds helder.
Besluit: In gevallen van eenzijdige limbale deficiëntie kan een transplantatie van gezond limbaal weefsel vanuit het normale andere oog resulteren in een stabiel cornea-oppervlak en een rustig en comfortabel oog. Transplantatie van een excentrische corneolimbale allogreffe onder algemene Ciclosporine A bescherming is een optie voor de rehabilitatie van patienten met ernstige bilaterale stamcel deficiëntie.

ZUSAMMENFASSUNG

Ziel: Die Vorzüge zu illustrieren der limbalen Stammzell Transplantation in drei Augen mit ernstliche oberflächliche Hornhautschaden nach chemischen Verbrennung.
Methoden: In zwei Patienten mit monocülärer Hornhautvernarbung und Vascularization durch chronische chemische Verbrennung, wurde ein Limbalgewebe Autogreffe transplantiert von anderem unverletztem Auge. Eine vollständige oberflächliche Keratektomie war vollstreckt ins Rezeptorauge. Der Patient mit bilateraler okulärer Oberflächebeschädigung hat eine dezentrierte korneolimbale Allogreffe erwerbet. Zum vermindern des Risikos auf immunologische Rejektion vom transplantierten Limbus wurde dieser Patient behandelt mit systemischer Verabreichung von Ciclosporin A.
Erfolge: Postoperativ erzeugten die Limbalautogreffen ein normales Epithelium des Rezeptorauges mit weniger Vascularization und Vernarbung. Unsere zwei Patienten erzeigten eine einsprichender Ausfall der Symptomen (Röte, Schmerzen, Lichtscheuheit) und ein besser Sicht. Die korneolimbale Allogreffe ist klar geblieben bis zu fünf Monate postoperativ.
Beschluss: In Fälle mit unilateraler limbaler Defizit, resultiert Transplantation gesunder Limbalgewebe des normales Auge in eine stabile okuläre Oberfläche des verletzten Auge. Patienten mit ernstlichen bilateralen Stamzelldefizit wurden durch eine dezentrierte korneolimbale Allogreffe rehabilitiert unter Deckung von Ciclosporin A.

KEY WORDS

Limbal stem cell - Limbal transplantation - Ocular surface failure

MOTS CLES

Cellule souche limbique - Transplantation limbique - Déficience épithéliale cornéenne

INTRODUCTION

Limbal transplantation is based on the concept that the limbus contains self-renewing cells (3,9,10). They are located in the basal limbal epithelium, straddling the limbus 0.5 mm on to the cornea and 1.0 mm on to the perilimbal conjunctiva. The limbal epithelium is 10 to 15 cell layers thick and is broadest at the upper and lower limbal poles (13). It consists of radially oriented palisades of Vogt and intervening interpalisades (4). The interpalisades present a repository of replicating epithelial cells. The palisades of Vogt are fibrovascular ridges and serve to nourish the epithelial cells. The density in limbal stem cells gradually decreases from the upper and lower poles toward the horizontal. Limbal stem cell deficiency may be associated with specific disease entities like aniridia, Stevens-Johnson syndrome and ocular pemphigoid, or may be secondary to chemical injury, thermal injury, contact lens wear and surgery involving the corneosceral limbus (6,15). Transplanted limbal cells offer a new source of cells to resurface and stabilize the cornea (18), by a centripetal movement from the limbal area toward the central cornea.

Patients in whom limbal stem cell disease is unilateral are a candidate for a limbal autograft transplantation. Donor limbal tissue is then harvested from the healthy fellow eye.

Limbal allograft transplantation is an option in bilateral ocular surface disorders (19,21). In patients with bilateral stem cell deficiency long term rehabilitation can only be achieved by transplantation of donor limbal tissue. A variety of allograft procedures for epithelial transplantation have been investigated: separate limbal allograft transplantation, penetrating keratoplasty with oversize grafts and transplantation of an eccentrically trephined corneolimbal transplant. This last method is a one-step procedure with simultaneous penetrating keratoplasty in which about one third of the graft's circumference contains limbal area. The disadvantage of a heterologous source of tissue is the risk of rejection and the need for systemic immunosuppression.

Herein we present three patients with ocular surface disorder following chemical burns, who were successfully treated with limbal stem cell transplantation.

Fig. 1. Left, Failed graft after penetrating keratoplasty: unhealthy opaque corneal epithelium with recurrent erosions and stromal vascularization. Right, Fourteen months after limbal transplantation: normal epithelium grew on the recipient cornea with reduced vascularization. The result was a quiet and comfortable eye. The best corrected visual acuity was 12/100.

PATIENTS AND METHODS

REPORT OF CASES

Case 1

A 37-year-old woman sustained an ammonia alkali injury to the left eye ten years previously and underwent a penetrating keratoplasty two and a half years later. Following surgery the ocular surface failed to reepithelialize completely and a central epithelial defect persisted for 6 months (Fig. 1, left). Attempts to heal the defect with topical antibiotics, cycloplegics, intensive irrigation with physiological serum, and topical and systemic use of corticosteroids failed. Ptosis induction with Botulinum toxin was also unsuccessful. This resulted in a visual acuity of no more than hand movements closeby, and symptoms of ocular discomfort and pain necessitating daily intake of Efferalgan tablets. Nine and a half years after the original trauma, a corneal stem cell autotransplantation was performed using grafts from the normal fellow eye. The patient had a vision of 10/10 in the right eye and was initially understandably fearful of the operation. Postoperatively therapeutic soft contact lenses were placed on both eyes and topical therapy with Tobradex drops in the right eye, and Chloramphenicol drops without preservatives in the left eye were used. On the third day postoperatively Ultracortenol collyrium was associated in the left eye. Ten days after surgery complete epithelialization was documented, and 15 days after surgery the patient was asymptomatic with a visual acuity of 1/10. At the last visit more than one year after the transplantation, we saw a very thankful patient. There was no ocular irritation and the best corrected visual acuity was 12/100 (Fig. 1, right).

Case 2

A 41-year-old woman had suffered from an unilateral chemical burn with acetylsalicylic acid in 1984. After five months the eye had regained a vision of 5-/10. The following years she suffered chronic irritation of the eye, for which intermittent use of local NSAIDs and steroids was needed. In March 1998, intermittent topical administration of NSAIDs and corticosteroids was still necessary to reduce irritation and photophobia secondary to chronic corneal inflammation. The cornea showed a localized thinning and opacification, a 360- degree peripheral vascularization and limbal deficiency. We decided to perform an autologous limbal stem cell transplantation. The superficial vascularized tissue was completely removed from the right cornea. After surgery a therapeutic soft contact lens and Okacin collyrium were prescribed. Epithelialization was complete after 15 days. Unpreserved Dexamethasone 0.1% collyrium was instilled and gradually tapered. Six months postoperatively the patient was asymptomatic with a healthy epithelium and a clear cornea (Fig. 2). Visual acuity increased to 6/10.

Fig. 2. Fourteen years after an acid burn of the right cornea, an autologous limbal stem cell transplantation was performed. Six months later the patient was asymptomatic with a healthy epithelium and a clear cornea.

Case 3

A 52-year-old man suffered a bilateral ammonia alkali injury 22 years ago, resulting in a series of unsuccessful penetrating keratoplasties. The right eye had undergone four penetrating keratoplasties, and the left eye three. When we examined the patient in May 1997, visual acuity was light perception in the right eye and 1/10 with difficulty in the left eye. Both corneas showed stromal opacification, significant vascularization and an abnormal epithelium with calcareous deposits and several epithelial defects (Fig. 3,top left and right). The more severely scarred right eye underwent a triple procedure in October of that same year. As re-epithelialization had not occurred the fifth day postoperatively, a therapeutic soft contact lens was used. Topical therapy with cycloplegics and irrigation with physiological serum was prescribed and systemic Deltacortril 35 mg a day was started. Two weeks postoperatively the patient was again admitted to hospital because of a painful right eye with a raised intra-ocular pressure (+/-30 mmHg). Biomicroscopically there were 3 loosened sutures temporally and the cornea showed a total epithelial defect, a slight corneal haze, stromal infiltrates in the superior half and fine endothelial precipitates. At discharge from hospital the patient had a visu-

Fig. 3. Top left and right, Picture of the right and left eye 21 years after a bilateral alkali injury. The right eye had undergone 4 penetrating keratoplasties and a triple procedure. The left eye had undergone 3 keratoplasties. Bottom left, The right eye after corneolimbal allotransplant with a visual acuity of 4/10.

al acuity of counting fingers at 0.5 meter and the ocular pressure was controlled with Diamox per os. The right eye further deteriorated and showed evidence of a persistent epithelial defect with stromal opacification and peripheral vascularization. In June 1998 an eccentrically trephined corneolimbal allotransplant was performed from a cadaver donor eye. Despite intermittent raising of the intra-ocular pressure the postoperative evolution was favourable and visual acuity had improved from counting fingers to 4/10 (with a correction of +2D cyl -7D axis 140°). From the day of surgery systemic steroids and Ciclosporin A were administered to reduce the risk of allograft rejection. Medrol was given at a dosage of 32 mg on the day of surgery, and gradually tapered afterwards. Ciclosporin A was taken orally, aiming at blood levels between 100 and 150 ng/ml. The daily dosage varied between 300 and 650 mg, divided over two intakes with an interval of 12 hours. During the whole application period, nephrological monitoring was performed. The drug was well tolerated and there were no side effects. The local therapy consisted of unpreserved Dexamethasone and Scopolamine drops. Diamox tablets and Timoptol drops were given to keep the eye pressure under control. From 2 weeks after surgery on, a fine coating on Descemet's membrane was noted but the graft remained clear (Fig. 3, bottom left). The eleventh week postoperatively a combined epithelial and endothelial acute graft rejection episode occurred. Slitlamp examination showed the known Descemet stippling inferiorly, a slight central corneal oedema, and finally a raised oval line across the centre of the cornea. We suspected the patient of irregular intake of Ciclosporin A leading to a subtherapeutic blood-level of 49 ng/ml. The patient was referred to internal medicine for general and nephrological check-up, and the dosage of Ciclosporin was adjusted. The rejection line moved slightly more centrally and the Descemet stippling became less pronounced as Ciclosporin A levels returned to therapeutic levels. At the last visit, 5 months after limbal transplantation, the rejection line was still present. The graft remained clear and there were no signs of inflammation. Visual acuity was 4/10.

DISCUSSION

Chemical injuries to the corneal surface may lead to limbal damage. Extensive destruction of the limbal epithelium results in corneal epithelial break-down followed by conjunctival-epithelial invasion of the cornea.. This results in ocular surface failure with persistent epithelial defects, anterior stromal opacification, vascularization and thinning of the cornea (1,15,22).

Attempts to heal the compromised ocular surface with conventional medical management usually fail. Different surgical procedures have been developed aiming at replacing the limbal stem cells (7,8,9,12,13,22).

In unilateral ocular surface disease, transplantation of healthy limbal tissue from the normal fellow eye may result in a stable ocular surface and a comfortable eye (5,11,13). The favourable results obtained with limbal autograft transplantation in our two patients confirm the results of other surgeons (8,13,18,22).

However in patients with bilateral ocular surface disease limbal allograft transplantation may become necessary to restore visual function. Because the limbal area includes many antigen-presenting cells, the risk of rejection is high and strong systemic immunosuppression becomes necessary (14,16,17,20). In our patient a limbal allograft transplantation was performed using an eccentrically trephined corneolimbal donor graft protected by systemic immunosuppression with steroids and Ciclosporin A. With this procedure we were able to reconstruct a stable corneal epithelium with concomitant improvement in visual acuity. Despite immunosuppression endothelial and epithelial rejection occurred in our patient. However this rejection reaction could be successfully reversed by raising the Ciclosporin intake.In the future further progress in the success of limbal allografting may be expected from the combination of systemic Ciclosporin A prophylaxis and more effective HLA matching (2,14).

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